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# An Experimental Study of the Role of the Vagus Nerve in the Pathogenesis of the Dumping Syndrome —Hemodynamic Aspects in the Microcirculation of the Intestine—

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## Introduction

Although the role of the vagus nerve in the pathogenesis of the dumping syndrome has been the subject of research and discussion for a long time, there are still many unknown aspects causing disagreement among the various investigators<sup>9)10)27)32)36)</sup>.

ISHIGAMI<sup>23)</sup>, on the basis of KIMURA's suggestion, invented a new type of operation, a total gastrectomy with preservation of the hepatic and posterior celiac vagi. After this type of gastrectomy, the dumping syndrome occurred more frequently, although postoperative complications such as malnutrition were markedly decreased, as compared with those in the conventional total gastrectomy with truncal vagotomy<sup>13)14)24)25)</sup>. This finding suggests that there is a close relationship between the etiology of this syndrome and the celiac vagi.

WAKABAYASHI<sup>48)49)</sup> and TOSHIMITSU<sup>46)</sup>, experimentally and clinically, studied the general hemodynamics and the serotonin (5-Hydroxytryptamin, 5-HT) metabolism in response to intrajejunal hypertonic glucose and clarified in part the mechanisms that the severing of the posterior celiac vagi suppressed in the occurrence of this syndrome.

It is a generally accepted theory that the rapid passage of relatively undiluted food into the proximal small intestine after gastric surgery can initiate the dumping syndrome by causing decrease in circulating plasma volume<sup>20)50)</sup>, release of humoral factors<sup>26)52)</sup>, disturbances of the intestinal microcirculation<sup>38)</sup> and stimulation of the autonomic nerve<sup>19)37)</sup>.

Following the description of BERK and associates<sup>3)</sup>, YAMAGISHI and his group<sup>38)42)52)</sup> found, on direct observation, marked microcirculatory disturbances of the mesenteric and intestinal walls and an elevation on the portal venous oxygen saturation after intrajejunal glucose administration. They theorized that these microcirculatory disturbances were a primary factor in the mechanism that initiates this syndrome. Thus, if the effect of celiac vagotomy on the microcirculation of the intestine during experimental dumping is clarified,

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Key words : Dumping syndrome, Microcirculation, Vagotomy, Portal venous oxygen saturation, Vascular permeability

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it may be a key to elucidate the role of the vagus nerve in the pathogenesis of the dumping syndrome. However, no study has been done from this point of view, except LIN's report<sup>28)</sup> on portal hemodynamics.

The present study was designed to evaluate the effect of the severing of the celiac vagi upon intestinal microcirculatory disturbances during experimental dumping. Morphological observation and measurement of the portal venous oxygen saturation were the means of evaluation. The effects of autonomic nerve blocking agents upon microcirculation during experimental dumping were studied also.

### Materials and Methods

#### A. Observation of the microcirculation of the intestine

##### 1. Preparation of animals

Male albino rats of the Wister strain weighing from 150 to 230g were anesthetized with ether. The animals were deprived of food for at least 24 hours prior to the experiment but had free access to water.

They were divided into three groups : non-vagotomized group (control), vagotomized group (subdiaphragmatic posterior truncal vagotomy, 7 days prior to the experiment), and atropinized group (Atropine sulfate, 1.0 mg/kg intramuscularly, 30 minutes prior to the experiment). Each group was given the dumping stimulus and the microcirculatory disturbances of their intestines were studied.

In addition, during the experimental dumping, the effects of intramuscularly administered reserpine (Apoplone, 10 mg/kg, 4-24 hours prior to the experiment) and intraluminally administered lidocaine (1% Lidocaine hydrochloride, 10 ml/kg, for 20 minutes just prior to the dumping stimulus) were studied.

After the jejunum was ligated approximately 5 cm distal to the Treitz ligament, the dumping stimulus was given by a rapid (10 sec.) injection of 10 ml/kg of 50% glucose into the jejunum, just distal to the ligature.

##### 2. Observations of the microcirculation

i) Direct observations of the microcirculation in rat mesentery were made according to ZWEIFACH's method<sup>54)</sup>.

A loop of distal ileum was withdrawn from the peritoneal cavity through a short midline incision on the lower ventral abdominal wall. A suitably vascularized area, where minute vessels formed vascular networks on the mesentery, was kept moistened with Ringer's solution while the rat was laid on its left side on a special animal board which had a large glass slide on one side. This board was set on the mechanical stage of an ordinary microscope (Nicon SR) equipped with a moist chamber warmed to body temperature.

After the four points of WEIS-FOGH<sup>51)</sup> were checked for disturbances in microcirculatory flow, microscopic observations were made with transillumination by a substage condenser. Vascular changes were recorded photomicrographically on 35-mm film using a Nikon-F

camera.

ii) Observations of the microcirculation in the intestinal wall

a) Dry ice methanol wintergreen method (DMW method)<sup>41)</sup>

Two ml of India ink were injected into the aorta through a left thoracotomy 20 minutes after instillation of hypertonic glucose into the jejunum just distal to the ligature. Biopsy samples were excised from two different levels of the intestine: proximally 5 cm above the ligature and distally 5 cm below the ligature.

The samples were immediately frozen in methanol cooled by dry ice and gradually (over a 4-day period) returned to room temperature. Then they were dipped into oil of wintergreen (Methyl salicylate) to make them transparent, were carefully sectioned and, without staining, were observed microscopically.

b) FITC-Dextran method<sup>30)</sup>

Two ml of 10w/v% FITC-Dextran (Fluorescein isothiocyanate dextran, molecular weight approximately 39,000) were injected into the jejunum. Five minutes later, intestinal samples were rapidly frozen in isopentane cooled by dry ice acetone and then freeze-dried for 5 days. These specimens were embedded in paraffin and cut into sections approximately 10 $\mu$  thick.

An Olympus FLM fluorescence microscope with filters was used for the observations (excitation filter: B2, Barrier filter: Y52).

For the photographs of the intestinal specimens, Ectachrome film was used.

iii) Changes in vascular permeability of the intestine

a) A fluorohistochemical study

A stock solution of an Evans blue-albumin complex (E-A complex) was prepared by dissolving 0.6g of Evans blue and 4g of bovine serum albumin in 100 ml of normal saline, which was shown by NICOLYSEN and STAUB<sup>33)</sup>.

Immediately after the intravenous injection of E-A complex solution, the dumping stimulus was given. Twenty minutes later, tissue samples from the intestine were removed. Each tissue sample was frozen in dry ice acetone and then freeze-dried at  $-35^{\circ}\text{C}$  for 4 days. The freeze-dried tissues were then prepared, mounted and examined with the same fluorescence microscope.

b) Quantitative extraction of Evans blue from intestinal contents

The abdomen was opened by a midline incision after the intravenous injection of 10ml/kg of E-A complex, and two ligatures, in the duodenum just below the pylorus and in the jejunum approximately 20 cm below the Treitz ligament, were tied to make an intestinal segment. A hypertonic glucose solution was instilled into this segment through the duodenum. Twenty minutes later, the segment was removed and its contents collected in a test tube. Extraction and determination of the amount of Evans blue in the contents were done according to HARADA's method<sup>18)</sup>. The quantity of Evans blue was estimated with a Hitachi spectrophotometer (139 UV-VIS Spectrophotometer).

The groups were analysed by Students "t" test for significant difference.

## B. Measurement of portal venous oxygen saturation

### 1. Preparation of animals

Healthy, fasting adult mongrel dogs weighing 8 to 18 kilograms were anesthetized with sodium pentobarbital (Nembutal, 30 mg/kg intramuscularly) after induction with ketamine (Ketalar-50, 200 mg intramuscularly). Ventilation was accomplished through a cuffed endotracheal tube and a mechanical respirator, using compressed air.

The dogs were divided into four experimental groups: non-vagotomized group (control); vagotomized group (posterior celiac vagotomy, 2 weeks prior to the experiment); atropinized group (Atropine sulfate, 0.3 mg/kg intramuscularly, 40 minutes prior to the experiment) and reserpinized group (Apoplone, 0.5 mg/kg intramuscularly, 24 hours prior to the experiment).

The abdomen was opened with a midline incision. For the sampling of portal blood, the splenic vein was cannulated with an 18-gauge polyethylene catheter inserted into the portal vein, the tip lying immediately proximal to the bifurcation of the portal vein. For the arterial blood, a teflon tube (Venula G 19) was placed in the femoral artery. After a 40-minute stabilization period, blood samples from the portal vein and the femoral artery were drawn before and 5, 10, and 30 minutes after instillation of hypertonic glucose through a Nélaton catheter introduced into the duodenum.

### 2. Method of analysis

PH and oxygen tension ( $P_{O_2}$ ) of the portal venous blood and the arterial blood were measured with a blood gas analyzer (Corning Model 160 or Radiometer Model ABL 1). Each value for oxygen saturation was calibrated with a nomogram.

The results were analyzed using an analysis of variance.

## Results

### 1. Direct observation of the mesenteric circulation of rats

In the non-vagotomized control group, many of the mesenteric venules showed retardation of flow, stagnation and agglutination of blood cells immediately following instillation of hypertonic glucose into the small intestine. After several minutes, stasis, sludging and plasma skimming appeared and then backflow in the opposite direction was seen in the mesenteric microarteries (Fig. 2). Some of these problems were communicated directly to unchanged bigger venules through arteriovenous anastomosis (AVA).

However, in the vagotomized group, after instillation of glucose, severe disturbances of the microcirculation, such as sludging and stasis, were rarely observed but there was occasional venular retardation (Fig. 4). No difference in mesenteric circulation between the non-vagotomized group and the vagotomized group was seen prior to the instillation of hypertonic glucose into the intestine (Fig. 1, 3).

In the atropinized group, only temporary mild disturbances were seen, similar to the findings in the vagotomized group (Fig. 5, 6).

### 2. Observations of the microcirculation in the intestinal wall

## i) DMW method

After the dumping stimulus, in the non-vagotomized group, the India ink barely reached the base of the villi capillary networks (Fig. 9, 10, 11). When there were severe disturbances of the microcirculation, the flow disturbance extended not only to the capillary networks of the villi but also to the submucous vascular plexus.

In the vagotomized group, since the India ink usually reached the villi tips, it was concluded that microcirculatory changes induced by the dumping stimulus were relatively mild or completely absent (Fig. 12, 13).

In the atropinized group (Fig. 14), the reserpinized group (Fig. 15) and the lidocaine group (Fig. 16), microcirculatory disturbances of the intestinal wall were comparatively mild, also.

## ii) FITC-Dextran method

The findings for these specimens were similar to those of the DMW method, except for the exudation of FITC-Dextran into the intestinal lumen (Fig. 15, 16). In the DMW method it was necessary to inject India ink rapidly into the aorta, after thoracotomy, in order to get a good contrast. These procedures might have had some effect on the hemodynamics of the intestinal microcirculation. However, morphologically, no difference between

**Table 1.** Effects of vagotomy and atropine on rat mesenteric microcirculation after instillation of hypertonic glucose into the intestine

	Non-vagotomized Group	Vagotomized Group	Atropinized Group
Venules and capillaries			
Flow			
Retardation	+++	++	+
Stasis	+++	—	—
Caliber			
Dilation	+++	+	+
Blood cells			
Stagnation	+++	++	+
IEA Rouleaux formation	+++	—	—
Sludging	+++	—	—
Plasma skimming	+++	—	—
Arterioles			
Flow			
Retardation	++	+	+
Stasis	++	—	—
Regurgitation	++	—	—
Caliber			
Dilation	—	—	—
Blood cells			
IEA Rouleaux formation	++	—	—
Sludging	++	—	—
Plasma skimming			
Vasomotion of vessels			
Disappearance	+	—	—

IEA : intravascular erythrocyte agglutination

the findings of the FITC-Dextran method without thoracotomy and those of the DMW method with thoracotomy. Consequently, it was concluded that thoracotomy and the puncture of the aorta do not significantly affect the microcirculatory system of the intestine.

### 3. Changes in permeability of the intestine

#### i) Fluorohistochemical study

In the non-vagotomized group, a brilliant red-orange fluorescence of Evans blue occurred in the intraluminal contents and in the wall of the intestinal segment exposed to the hypertonic glucose solution. This fluorescence was strongest in the luminal contents and in the interstitium of the villi tip region and almost as strong in the villi blood vessels. There was little fluorescence in the interstitium of the villi base or in the cryptic layer (Fig. 20).

**Table 2.** Oxygen saturation of the portal blood and the arterial blood (%)

			Before	After 5'	10'	15'	30'
Non-vagotomized Group	1	P. V.	83	88	90	91	85
		F. A.	99	99	99	99	98
	2	P. V.	57	64	66	67	69
		F. A.	99	99	99	98	98
	3	P. V.	82	84	77	79	79
		F. A.	98	98	98	98	98
	4	P. V.	72	79	77	78	82
		F. A.	97	97	97	96	96
	5	P. V.	75	86	88	86	79
		F. A.	99	99	99	99	99
Vagotomized Group	1	P. V.	69	69	55	45	58
		F. A.	99	99	99	99	99
	2	P. V.	95	87	94	94	97
		F. A.	100	100	100	100	100
	3	P. V.	86	74	81	82	78
		F. A.	99	98	98	98	98
	4	P. V.	89	90	87	83	86
		F. A.	98	99	98	98	98
Atropinized Group	1	P. V.	81	82	77	75	66
		F. A.	99	99	99	99	99
	2	P. V.	89	82	85	85	81
		F. A.	99	99	99	99	98
	3	P. V.	82	81	74	73	64
		F. A.	98	98	98	98	98
	4	P. V.	92	89	85	71	71
		F. A.	97	98	97	98	98
	5	P. V.	78	73	59	56	35
		F. A.	97	97	97	96	97
Reserpinized Group	1	P. V.	80	78	74	68	57
		F. A.	99	98	99	99	99
	2	P. V.	85	62	72	59	59
		F. A.	99	99	99	99	99
	3	P. V.	84	82	75	75	72
		F. A.	99	99	99	99	99

P. V. portal venous blood

F. A. : femoral arterial blood

The vagotomized and atropinized samples exhibited the identical fluorescent distribution as the non-vagotomized samples did, except that the non-vagotomized samples showed a greater fluorescent intensity (Fig. 21, 22).

The samples taken from the intestinal segment which was not exposed to the hypertonic glucose solution revealed no extravasation of the Evans blue-albumin complex (Fig. 19).

There were no differences among the three groups (the non-vagotomized, the vagotomized and the atropinized) in findings for the samples taken from the portion which was not exposed to the hypertonic glucose solution.

## ii) Quantitative extraction of Evans blue from the intestinal contents

As shown in Fig. 23, in the non-vagotomized control group, the value of Evans blue effluxed into the intestinal lumen was  $1.60 \pm 0.20$  (mean  $\pm$  1SE) mg/g wet tissue in the non-vagotomized control group,  $0.95 \pm 0.09$  mg/g w.t. in the vagotomized group and  $0.79 \pm 0.12$

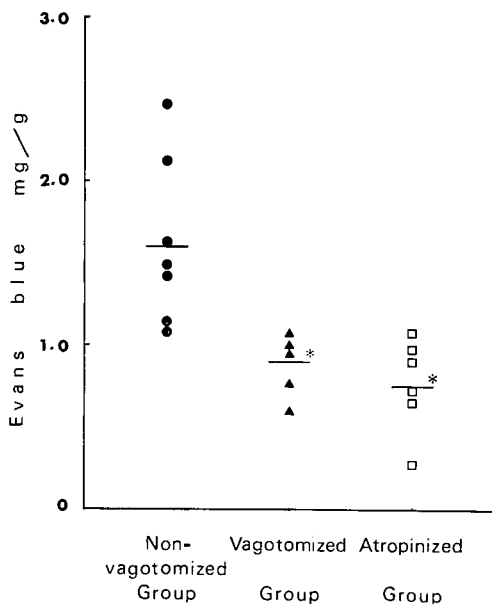


Fig.23. The value of Evans blue in the intestinal contents 20 minutes after instillation of hypertonic glucose.

Values in the non-vagotomized group (control) rose to a higher mean than in the vagotomized and atropinized group.

\* $p < 0.05$  vs non-vagotomized group

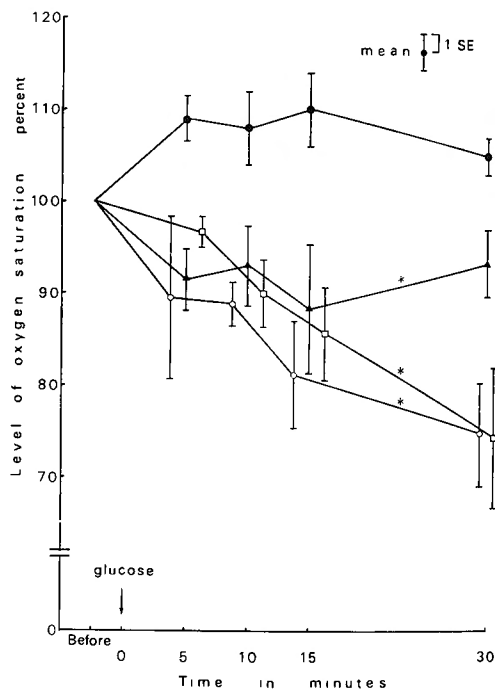


Fig.24. Level of oxygen saturation of portal blood before and after instillation of hypertonic glucose into the intestine. Each value is expressed as percent of the value of oxygen saturation before instillation of glucose.

Each curve represents a mean  $\pm$  standard error in non-vagotomized control dogs (●), vagotomized dogs (▲), atropinized dogs (□), and reserpinized dogs (○) during the 30-minute experimental period. \* $p < 0.05$  vs non-vagotomized dogs (control)



mg/g w.t. in the atropinized group. There was a significant difference between the non-vagotomized group and the other two groups ( $p < 0.05$ ).

#### 4. Changes in the portal venous oxygen saturation

In the non-vagotomized group, the level of portal venous oxygen saturation showed a tendency to rise after intraduodenal instillation of hypertonic glucose and to maintain the higher level during the 30-minute experimental period. On the contrary, the level of oxygen saturation decreased in response to the dumping stimulus in the other three groups, as illustrated in Fig. 24. The oxygen saturation of the femoral arterial blood in all four groups was unchanged or fell slightly (within 1%) during the experimental period (Table 2).

### Discussion

BERK and associates<sup>3)</sup> demonstrated that a rapid and highly significant rise in portal venous oxygen tension followed instillation of hypertonic glucose into the jejunum, and suggested that the opening of multiple visceral AVA in the small intestine played an important role on the early phase of the dumping response.

Subsequently, YAMAGISHI and his group<sup>38)42)52)</sup> found venous stagnation and opening of AVA on direct observation of the mesenteric capillary circulation, and also demonstrated that portal venous oxygen saturation rises during the dumping response. From these data they deduced the close relationship between the occurrence of the dumping response and the mechanism of microcirculatory disturbances to be as follows.

The rapid introduction of hypertonic solution into the upper intestine gives rise to a shift of fluid from the intestinal capillary blood into the lumen of the small intestine secondary to the rapid elevation of the intraluminal osmotic pressure. This fluid shift causes rapid hemodynamic changes such as sludging and opening of AVA in the mesenteric and intestinal capillary beds, resulting in tissue hypoxia in the intestine. This tissue hypoxia initiates, directly and indirectly, excessive reflex activity of the autonomic nervous system and abnormal release of some humoral factors, and soon the intricate symptoms of the dumping syndrome occur. Thus, they concluded that such microcirculatory disturbances and tissue hypoxia might be the primary initiating factors in the mechanism of the dumping syndrome.

FUKUI<sup>16)</sup>, in canine experiments, found that a significant elevation of portal venous oxygen tension occurred soon after hypertonic glucose instillation into the small intestine and suggested that this opening of the submucosal AVA was an important factor in the mechanism of the dumping syndrome. Since SPANNER<sup>39)</sup> described the submucosal AVA of the intestine, there has been no satisfactory explanation for its physiological role<sup>6)</sup>. In direct observation of the mesenteric microcirculation by SHOGIMEN<sup>38)</sup> and the author, the anatomical opening of AVA during experimental dumping was not observed until severe disturbances of the microcirculation, such as stasis of venular circulation and microarterial backflow, occurred. Therefore, it is likely that the opening of AVA in response to the dumping stimulus is not primary but secondary to severe disturbances of the microcirculatory flow

and plays a role as a safety valve in peripheral microcirculatory disturbances of the intestine.

In the present experiments as well as in the reports of YAMAGISHI and his group<sup>38)42)52)</sup>, serious microcirculatory disturbances of the mesentery and the intestinal wall, especially the mucosa (Fig. 2, 9, 10, 11) and a prolonged rise of portal venous oxygen saturation were found in the non-vagotomized group following the dumping stimulus (Fig. 23). In all the dumping experiments induced by instillation of hypertonic glucose into the intestinal lumen, the intestine was filled with a large amount of fluid and markedly distended by the end of the experimental period. These findings may have resulted from a shift of fluid into the intestinal lumen following a rapid increase in the vascular permeability of the intestinal wall after instillation of hypertonic glucose.

It can also be readily deduced that intraluminal accumulation of such a large amount of fluid may produce a decrease in the circulating plasma volume<sup>20)50)</sup>, a distension of the intestine<sup>19)21)</sup> and a traction on the mesentery<sup>8)</sup>, which have been regarded as important factors in the genesis of the dumping syndrome.

In animal experiments using  $^3\text{HOH}$  as a tracer, TOMODA and his coworkers<sup>45)</sup> discovered that  $\text{H}_2\text{O}$  shifted from the circulating blood stream into the intestinal lumen immediately after intrajejunal instillation of hypertonic glucose and that the decreased volume in the circulating blood was almost equivalent to the increased volume of intestinal fluid.

The present fluoromicroscopic study using the E-A complex showed changes in the permeability characteristics of the intestinal capillary wall following the dumping stimulus.

It was discovered that efflux of the E-A complex into the intestinal lumen occurred exclusively across the villi tip region and not across the cryptic layer (Fig. 20-22).

These findings are consistent with the observations of GRANGER and associates<sup>17)</sup> that the transmucosal albumin flux at elevated portal venous pressure occurs exclusively across the villi tip epithelium and not across the crypt epithelium, suggesting that this region is the structural locus for elevations in tissue pressure as compared to other regions in the intestinal mucosa.

In view of the presence of huge fenestrated capillary beds and the peculiar anatomical structure of the capillary network -hairpin loops- in the small intestinal villi<sup>12)</sup>, the exudation of a volume of water and albumin into the intestinal lumen during experimental dumping may be caused by hemodynamic changes in the microcirculation, as well as by the passive shift of water secondary to the difference in osmotic pressure between the intestinal tissue and the intraluminal contents. Consequently, it is theorized that the intestinal mucosa shows high vascular permeability induced by elevation of pressure in the venules and capillaries of the villi because of changes in the microcirculatory hemodynamics following instillation of hypertonic glucose.

Thus, microcirculatory disturbances induced by experimental dumping can be summarized as follows: 1) Morphological changes in the microcirculation of the intestinal wall, namely the mucosa, and the mesentery. 2) Increase of vascular permeability in the intestine.

3) Significant elevation of portal venous oxygen saturation and tissue hypoxia in the intestine.

The role of the autonomic nerve, especially the vagus nerve, in the dumping syndrome, has been noted by many investigators for many years.

SILVER and co-workers<sup>37)</sup> experimentally showed that severing of the mesenteric nerves to the challenged jejunum would completely prevent dumping responses.

WAKABAYASHI<sup>48)49)</sup> and TOSHIMITSU<sup>47)</sup>, in our laboratory, observed the frequent occurrence of the dumping syndrome after total gastrectomy with preservation of the hepatic and posterior celiac vagi and showed that a posterior celiac vagotomy suppressed the alteration of systemic hemodynamics and the release of 5-HT from the enterochromaffin cells into the portal venous blood stream.

LIN<sup>28)</sup> showed that elevation of the portal venous oxygen tension during truncal vagotomy suppressed the opening of AVA of the intestine following the dumping stimulus.

These observations indicate that truncal vagotomy may suppress the dumping response. The findings in the present study that morphological disturbances of the intestinal microcirculation were mild in the vagotomized group, in comparison with the non-vagotomized control group, support this theory.

Namely, in the non-vagotomized control group, stasis of the capillary blood flow of the villi, retardation and stagnation of mesenteric circulation and opening of AVA were demonstrated following instillation of hypertonic glucose into the intestine (Fig. 2). However, such microcirculatory disturbance in the intestinal wall and the mesentery tended to be suppressed in the vagotomized group (Fig. 3, 4, Table 1).

Also, it was found that the level of portal venous oxygen saturation rose following instillation of hypertonic glucose in the non-vagotomized control group, while it decreased significantly in the vagotomized group. These findings indicate that a celiac vagotomy abolishes or diminishes the opening of AVA during experimental dumping.

Moreover, it is suggested that, in view of the distinctive structures of the capillaries in the villi as previously mentioned, the suppression of the efflux of the E-A complex into the intestinal lumen following celiac vagotomy is a direct result of the reduction of microcirculatory disturbances in the intestinal wall.

There have been many differing reports concerning the effects of truncal vagotomy upon the superior mesenteric arterial flow and the intestinal and mesenteric microcirculation. However, BALLINGER and his group<sup>1)</sup>, PETER<sup>35)</sup>, ISHIGAMI<sup>22)</sup>, TOKURA<sup>44)</sup> and others, all reported that the blood flow of the superior mesenteric artery was decreased by truncal vagotomy at least for a short period. PADULA<sup>34)</sup> and BALLINGER<sup>2)</sup>, by direct observation, found a significant decrease of blood flow in the capillaries of the villi. Some investigators speculated that such decrease of the intestinal microcirculatory flow after vagotomy might be caused by the opening of AVA.

Therefore, it is possible that in vagotomized groups disturbances of microcirculatory flow have existed prior to dumping experiments. In the present study, however, micro-

circulation of the intestinal wall and the mesentery of rats 7 days after truncal vagotomy showed the same morphology as that of the non-vagotomized rats. Also, there was no significant difference in the level of portal venous oxygen saturation before instillation of hypertonic glucose between dogs 14 days after celiac vagotomy and non-vagotomized dogs (Fig. 7, 8, Table 2).

Consequently, it can be concluded that in this study the significant differences in response of the microcirculatory system between the non-vagotomized group and the vagotomized group were due to the rapid instillation of hypertonic glucose.

Moreover, the prevention or diminution of microcirculatory disturbances in the intestine, of rise in the portal venous oxygen saturation and of intraluminal efflux of albumin, occurred after the administration of atropine, a cholinergic nerve blocking agent, as well as after truncal or celiac vagotomy. These results suggest that the effect of a celiac vagotomy upon the dumping response may be caused by the severing of a cholinergic nerve fiber in the vagus nerve.

TEXTURE<sup>43)</sup> mentioned that microcirculatory changes during experimental dumping were controlled by humoral or neurogenic factors, and FUKUI<sup>16)</sup> suggested that these changes were closely related to the autonomic nerve and humoral agents such as catecholamine (CA) and 5-HT.

It has been found that blood flow in the superficial layer of the intestinal mucosa is gradually decreased by successive electrical stimuli to the sympathetic nerve as well as by the dumping stimulus. Also, it has been reported that the same changes were found in the mesentery, when the vagus nerve was electrically stimulated<sup>47)</sup>. Because the anatomical presence of sensory nerve receptors on the intestinal mucosal surface has not been proved, it is not known if a dumping stimulus applied to the mucosa is transmitted directly through nerve pathways to the microcirculation. However, participation of both nervous systems in the mechanism of microcirculatory disturbances following a dumping stimulus can not be completely negated.

Concerning humoral factors associated with the dumping syndrome, there have been many reports of transfusible agents since JOHNSON and JESSEPH's research<sup>26)</sup>.

DRAPANAS and associates<sup>11)</sup> reported that portal venous 5-HT level was elevated following instillation of hypertonic glucose into the proximal intestine and dumping responses occurred after administration of 5-HT into the portal vein. Recently, the participation of histamine, bradykinin<sup>53)</sup>, substance-P<sup>40)</sup> and GEP-hormones such as enteroglucagon<sup>5)</sup> and motiline<sup>40)</sup>, in dumping responses was demonstrated. Most of these humoral agents have vasoactive action. These findings suggest that there is a close relationship between such agents and microcirculatory disturbances during experimental dumping. 5-HT, particularly, is considered to be the most important agent as an initiating factor of response, because 5-HT is contained in the enterochromaffin cells distributed throughout the intestinal mucosa and is released into the tissues following a dumping stimulus, and because the local administration of 5-HT produces the same microcirculatory disturbances as those seen in experimental

dumping.

However, regarding the mechanism of 5-HT release during a dumping response, there are two theories which conflict with each other. One is that 5-HT is released into the tissues when the microvilli of the enterochromaffin cells are directly stimulated by hypertonic glucose which provokes the resulting microcirculatory disturbances. The other theory is that the microcirculatory disturbance occurs in advance and then 5-HT is released through the resulting tissue hypoxia.

In the present study, microcirculatory disturbances following the dumping stimulus were prevented or diminished by the administration of reserpine, which caused depletion of the central or peripheral stores of 5-HT and CA. These results seem to support the first of the above two theories. Microcirculatory disturbances during experimental dumping were also prevented by the intraluminal administration of lidocaine, which anesthetized the surface of the intestinal mucosa and the receptors in the intestinal wall. These results also seem to indicate that microcirculatory disturbances due to the dumping stimulus are induced by the release of 5-HT, considering MIYATA's observation<sup>31)</sup> that lidocaine suppresses the release of 5-HT during the dumping stimulus.

In recent studies<sup>16)48)</sup>, it was discovered that the release of 5-HT in experimental dumping was suppressed by celiac vagotomy, while 5-HT was released from the intestinal mucosa into the portal venous blood by electrical stimulation of the vagus nerve. Therefore, it is theorized that the decrease in microcirculatory disturbances during the experimental dumping observed in the present study, may have been the result of the suppression of the release of 5-HT after a celiac vagotomy.

Also, there are some recent reports that histamine-type mediators in large quantities, including 5-HT, may directly affect vascular smooth muscle and significantly change their resistance, thus, disturbing the microcirculatory flow. However, even in small quantities which are not enough to affect smooth muscles these mediators can increase vascular permeability through a large pore system.

Therefore it is reasonable to conclude that the suppression of efflux of the Evans blue-albumin complex in both vagotomized and atropinized groups is the result, at least in part, of the prevention of release of humoral factors, including 5-HT.

Portal venous 5-HT level is influenced by two factors, the concentration of 5-HT released into tissues and the local clearance of 5-HT, that is the act of removal of released 5-HT from intestinal tissue. This local clearance is usually determined by the local blood flow in the tissue. Consequently, no matter how high the 5-HT concentration in the tissue may be, portal venous 5-HT level will decrease if the volume of local blood flow decreases. However, in the present study, it was found that microcirculatory disturbances of the intestinal wall were more evident in the non-vagotomized group in spite of rises in 5-HT release in the tissues and in the portal venous 5-HT level. These results seem to contradict each other, since the portal venous 5-HT level should decrease when microcirculatory disturbances increase.

Following the dumping stimulus, however, portal venous 5-HT level reaches its maximum within 10 minutes.<sup>46)</sup> Therefore, the release of 5-HT can be deduced to occur in advance of microcirculatory disturbances.

Moreover, observations in our laboratory showed that the rate at which 5-HT disappeared from intestinal tissue during the 30 minute experimental period was  $23.60 \pm 5.32\%$  in the non-vagotomized group and  $3.53 \pm 1.47\%$  in the vagotomized group<sup>15)</sup>. Therefore, in the non-vagotomized group, even though the local clearance of 5-HT decreased due to increased microcirculatory disturbances, the portal venous 5-HT level was elevated because of a significant rise in the absolute quantity of released 5-HT. In the vagotomized group, in the contrary, in spite of increased local clearance of 5-HT, elevation of the portal venous 5-HT level was slight.

Since the blood flow of the microcirculation is well maintained near the crypt layer in which the enterochromaffin cells are distributed most thickly, it seems likely that there will be scarcely any difference in the local clearance of 5-HT between the non-vagotomized and the vagotomized groups in this region.

Summarizing the observations in the present study, the pathogenesis of microcirculatory disturbances of the intestine during experimental dumping is essentially identical with the pathogenesis of a rise in vascular permeability. Namely, it is theorized that these results occurred through nerve reflex and release of humoral factors produced by a rapid induction of hypertonic glucose into the intestine.

### Summary and conclusion

In order to clarify the relationship between the celiac vagi and the dumping syndrome, hemodynamic changes of the microcirculatory system of the small intestine of dogs and rats were examined after a dumping stimulus, the instillation of a hypertonic glucose solution into the intestinal lumen, was given. The following results and conclusions were obtained.

1. During the dumping response, in direct observation of the mesentery and in examination of the intestinal wall by the dry ice methanol wintergreen method, severe microcirculatory disturbances such as stasis, sludging and opening of AVA were seen in non-vagotomized rats, while only mild microcirculatory disturbances were seen in vagotomized rats.

2. Efflux of a large amount of Evans blue-albumin complex into the intestinal lumen occurred following the dumping stimulus in non-vagotomized rats. However, in vagotomized ones, efflux of Evans blue-albumin complex was small. The difference between the non-vagotomized and the vagotomized groups was statistically significant ( $p < 0.05$ ).

3. In non-vagotomized dogs, the portal venous oxygen saturation significantly rose in response to the dumping stimulus. Conversely, a decrease of portal venous oxygen saturation was found in vagotomized dogs after experimental dumping. These findings strongly suggest the fall in oxygen consumption of intestinal tissue secondary to microcirculatory disturbances

in the intestine.

4. During experimental dumping, microcirculatory disturbances were mild in rats after administration of atropine, a cholinergic blocking agent, as well as in vagotomized rats.

5. Microcirculatory disturbances were very mild in rats after intramuscular administration of reserpine or intraluminal administration of lidocaine. These findings suggest the close relationship between microcirculatory disturbances and the metabolism of serotonin and catecholamine, or the mucosal reflex during experimental dumping.

From the results of the present study, it may be concluded that microcirculatory disturbances in the intestine are significantly suppressed by the severing of the celiac vagi. Conversely, it can be postulated that microcirculatory disturbances can be caused by humoral factors and nerve reflexes suppressing normal reactions in the microcirculatory system of the small intestine.

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## 和文抄録

## 迷走神経とダンピング症候群

## ——微小循環の面からの検討——

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迷走神経のダンピング症候群における役割については、古くから注目されているにもかかわらず、現在なお不明な点が多い。

われわれは、迷走神経腹腔枝切断 (迷切) がダンピング症候群の発現を軽減防止することを迷走神経部分的保存胃全摘術後成績や全身循環動態および serotonin 代謝の面から明らかにしてきた。

ダンピング症候群の発現機序には、腸管系の微小循環障害が重要な役割を示すことが、Berk (1964年) 以来、強調されているので、実験ダンピングにおける腸管の微小循環障害におよぼす迷切の影響を明らかにすることは、ダンピング発現に関与する迷走神経の役割を解明する1つの鍵となると考えられる。

このような観点から本研究においては、実験ダンピングにおける腸管の微小循環障害におよぼす腹腔枝切断の影響を検討した。すなわちラット腸管における微小循環障害を生体顕微鏡観察法 (Zweifach 法)、瞬間凍結墨汁法 (DMW 法)、色素注入 (Evans blue-albumin complex, FITC-dextran) による蛍光組織化学的方法ならびに化学的定量法により検索するとともに、イヌを用いて、門脈血酸素飽和度の変動を検討した。さらに、このような微小循環障害に与える自律神経遮断剤などの効果を検討し、次のような成績および結論を得た。

1. 腸間膜微小循環の直接観察および DMW 法による腸管壁の検索で、ダンピング刺激後、非迷切群 (対

照群) では stasis, sludging, AVA の開放などの著明な血流障害が起るのに反して、迷切群では微小循環障害は非常に軽度であった。

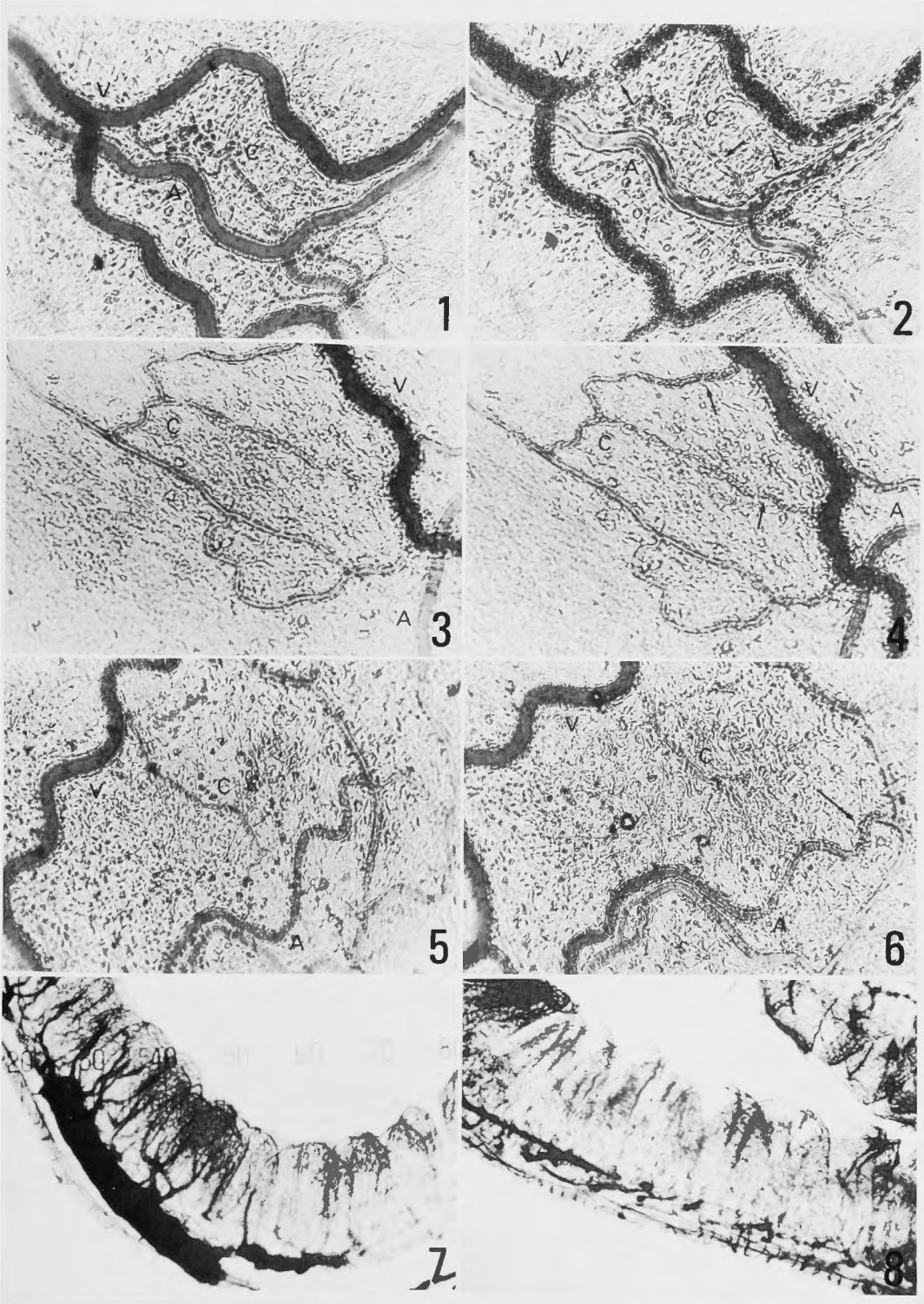
2. Evans blue-albumin complex の腸管内への漏出は、迷切群では  $0.95 \pm 0.089 \text{ mg/g}$  で、非迷切群の  $1.60 \pm 0.196 \text{ mg/g}$  に比べて、明らかに有意の低値を示した。

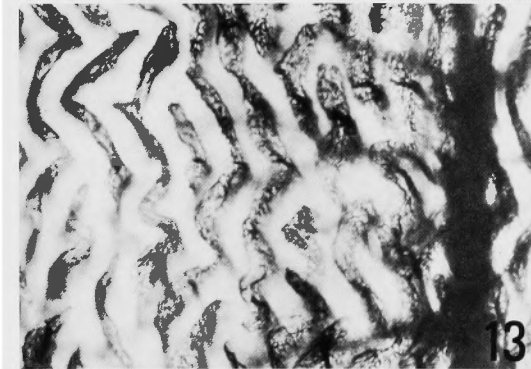
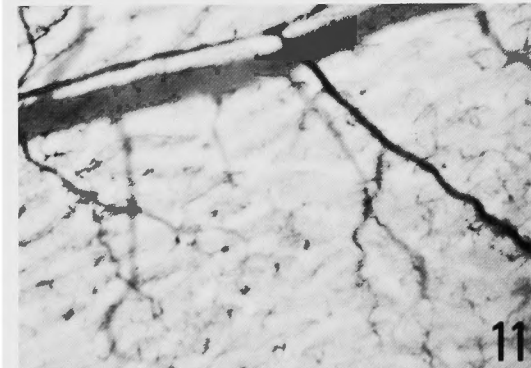
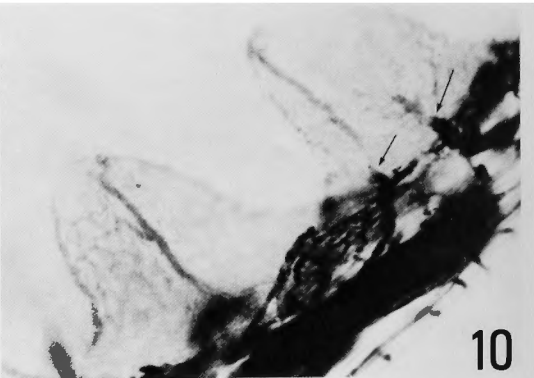
3. 門脈血酸素飽和度の測定でも、非迷切群では、ダンピング刺激後、酸素飽和度は上昇し、腸管での微小循環障害による酸素消費の低下が示唆された。これに対して、迷切群では逆に酸素飽和度は下降した。

4. コリン作動神経遮断剤である atropine ( $1.0 \text{ mg/kg}$ ) を前投与した場合は、迷切群と同様、微小循環障害は軽度であった。

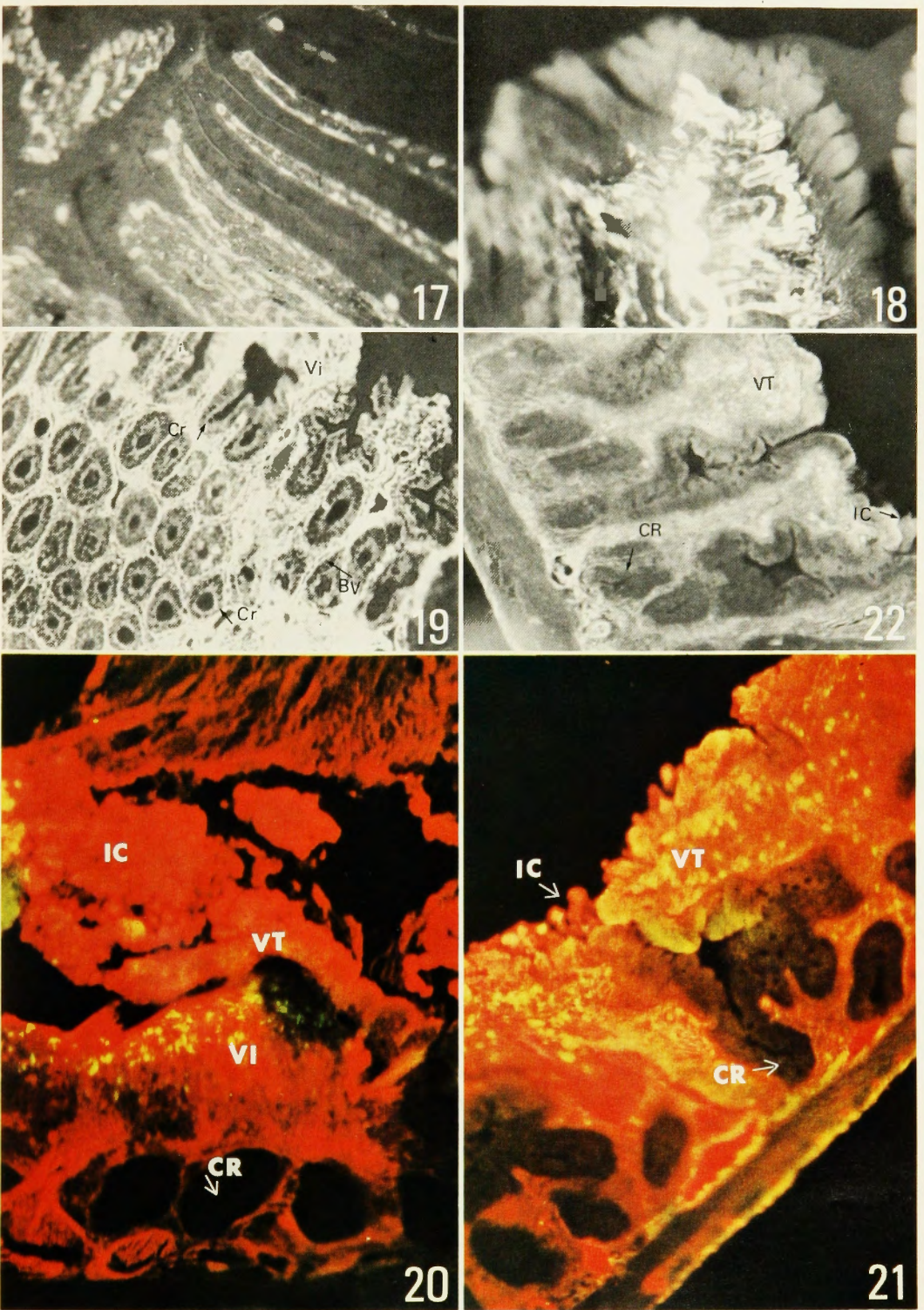
5. reserpine ( $10 \text{ mg/kg}$ ) の前投与や、1% 塩酸リドカイン ( $10 \text{ ml/kg}$ ) の腸管内投与の場合も、腸管の微小循環障害は著明に軽減した。このような所見は、実験的ダンピングにおける微小循環障害と serotonin や catecholamine 代謝、あるいは粘膜反射との密接な関係を示唆している。

以上の実験成績より、迷走神経腹腔枝切断は、実験ダンピングにおける腸管の微小循環障害を著明に軽減すると結論できるが、このような作用は、迷切が高張糖液に対する腸管の微小循環系の反応性を体液性因子または神経反射を介して抑制することによって発現されるものと考えられる。









## Explanation of Figures

Fig 1 to 7. Low power photomicrographs of networks of minute vessels which occupy mesenteric windows. A : Arteriole V : Venule C Capillary

**Fig 1.** Low power view of a portion of network of minute blood vessels in mesenteric window of non-vagotomized control rat, prior to the dumping stimulus, showing normal blood flow.

Arterioles, venules and capillaries are seen traversing thin space between mesothelial layers lining the mesentery.

The stream of red cells appears homogenous and the inner lining of the vessels is sharp and without white cells, and there is a clear layer of plasma between the vessel wall and the more axial stream of red cells. In the capillaries, the blood cells pass as single cells or as a string in single file.  $\times 100$

**Fig. 2.** Same field as in Fig. 1. Fifteen minutes after the dumping stimulus, showing typical dumping response.

Complete stasis of flow and sludging in venules and rouleaux formation and plasma skimming (arrows) in arterioles and capillaries are seen. Venules and capillaries are dilated maximally, and vasomotion is disappeared entirely in this stage.  $\times 100$

**Fig. 3.** Mesenteric vessels of rat 1 week after posterior celiac vagotomy prior to the dumping stimulus, showing normal blood flow.

Note that there is a clear peripheral layer of plasma in venules as well as in arterioles.  $\times 100$

**Fig. 4.** Same field as in Fig. 3. Fifteen minutes after the dumping stimulus. Slight retardation of venular flow and stagnation of blood cells in capillaries are seen (arrows). Vasomotion is kept satisfactory.  $\times 100$ .

**Fig. 5.** Mesenteric vessels 40 minutes after administration of atropine, prior to the dumping stimulus, showing normal blood flow as well as in Fig. 1. and Fig. 3.  $\times 100$ .

**Fig. 6.** Same field as in Fig. 5. Fifteen minutes after the dumping stimulus. Retardation of flow and stagnation in venule (arrow) are seen. Venules are dilated slightly and vasomotion is not disturbed.  $\times 100$ .

Fig. 7 to 15. Low power photomicrograph of rat intestinal section prepared by dry ice methanol wintergreen method.

**Fig. 7.** Cross section of intestinal wall of non-vagotomized control rat prior to the dumping stimulus, showing normal vascular pattern. Note that India ink is present in the capillary networks of intestinal villi.  $\times 40$ .

**Fig. 8.** Tangential view of a whole mount of intestinal wall of non-vagotomized control rat prior to the dumping stimulus, showing the normal vascular pattern.

Note that India ink is present in capillary networks of the villi as well as in submucosal vessels.  $\times 40$ .

**Fig. 9.** Cross section of intestinal wall of vagotomized rat prior to the dumping stimulus, showing normal vascular pattern. India ink are seen in capillary networks of intestinal villi as well as in the control rat (Fig. 7).  $\times 40$ .

**Fig.10.** Cross section of intestinal wall of a non-vagotomized control rat 15 minutes after the dumping stimulus, showing typical vascular pattern of the dumping response. India ink can not be seen in the capillary networks of the intestinal villi, but in the submucosal vascular plexus.  $\times 40$ .

**Fig.11.** Higher power view of Fig. 8. showing complete occlusion of axial arterioles of villi (arrows).  $\times 40$ .

**Fig.12.** Tangential view of a whole mount of intestinal wall of non-vagotomized control rat 15 minutes after the dumping stimulus, showing a typical vascular pattern of the dumping response. India ink is present in submucosal arteries, but not in capillary networks of the villi.  $\times 40$ .

**Fig.13.** Cross section of intestinal wall of a vagotomized rat 15 minutes after the dumping stimulus. Note that the India ink reaches the villi tips. This figure shows prevention of the dumping response by the vagotomy.  $\times 40$ .

**Fig.14.** Cross section of intestinal wall of an atropinized rat 15 minutes after the dumping stimulus.  $\times 40$ .

**Fig.15.** Cross section of intestinal wall of a reserpinized rat 15 minutes after the dumping stimulus.

×40.

- Fig.16.** Cross section of intestinal wall of lidocaine-administered rat 15 minutes after the dumping stimulus. ×40.

Fig. 14-16 show normal vascular pattern of villi as well as in Fig. 13.

Fig. 17 to 18. Low power photomicrograph of fluorescing section of intestinal villi of rat 5 minutes after injection of FITC-dextran.

- Fig.17.** Longitudinal section of intestinal wall of vagotomized rat prior to the dumping stimulus. The intense yellow fluorescing FITC-dextran is confined to capillary networks of villi. The interstitial tissue shows a green-yellow autofluorescence typical of normal intestinal tissue. ×100.

- Fig.18.** Cross section of intestinal wall of vagotomized rat 15 minutes after the dumping stimulus. FITC-dextran are seen in the capillary networks of the villi and in the interstitium of the villus tip region. ×200.

Fig. 19 to 22. Low power photomicrograph of fluorescing section of rat intestinal wall 20 minutes after injection of Evans blue-albumin complex. CR : Crypt VI : Villus VT : Villus tip region BV Blood vessel IC Intestinal contents

- Fig.19.** Photomicrograph of a fluorescing oblique section of the intestinal villi of non-vagotomized control rat prior to the dumping stimulus.

The bright red fluorescing Evans blue-albumin (bright white in this photo.) is confined to the vessels. The interstitial tissue shows a green-yellowish autofluorescence (dark in this photo.) typical of normal intestinal tissue. There is no fluorescence in the intestinal lumen (black in this photo).

- Fig.20.** Fluorescing cross section of the intestinal wall of non-vagotomized control rat 15 minutes after the dumping stimulus, showing typical dumping response.

Interstitial tissue and epithelium, especially at the villus tip region, and intestinal contents show an Evans blue-albumin fluorescence (bright red) nearly as intense as that of the contents in blood vessels. But, there is no Evans blue-albumin fluorescence in the cryptic layer (arrow), which shows only a normal green autofluorescence. ×100.

- Fig.21.** Cross section of intestinal wall of vagotomized rat 15 minutes after the dumping stimulus. There is moderate Evans blue-albumin fluorescence in interstitium, especially at the villus tip region. There is also weak Evans blue-albumin in the intestinal contents (arrow). ×100.

- Fig.22.** Cross section of atropinized rat after the dumping stimulus. There are intense Evans blue-albumin fluorescence in the capillary networks of the villi and weak fluorescence in the interstitial tissue as well as in Fig. 21. ×200.